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Potential Roles of miR-106a in Breast Cancer

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1. Introduction

The discovery of interfering RNAs uncovered a new level of regulation of gene expression. It is now believed that as much as 92% of gene expression may be regulated by interfering RNAs. Interfering RNAs may be micro RNAs (miRNAs) or small interfering RNAs (siRNAs). Our focus is on miRNAs. These are mostly coded in intronic or intergenic regions of DNA and are grouped into families on the basis that they likely evolved from a common ancestral gene. Among the miRNA families, the miR17-92 family has attracted attention because of its oncogenic activity. miRNAs in this family include the miR17-92 cluster and two paralogs, the miR-106a and miR-106b clusters. Expression of these miRNAs is markedly upregulated in several types of cancer, and they are considered oncomirs. The two paralogs derive from an ancient gene duplication event involving the miR17-92 cluster. They therefore share highly similar sequences with miR17-92 family members and each other. As a result, they also work on very similar targets, primarily inhibiting the translation of target mRNAs by binding to the 3′ untranslated region. The miR-106 paralogs are located on different chromosomes from the miR17-92 cluster: miR-106a is intriguingly located on the X chromosome, miR-106b on chromosome 7, and miR17-92 on chromosome 13. Regulation of expression of any of the paralogs can therefore occur without concomitant regulation of the other two. This review examines the thesis that miR-106a in particular may play an important role in the development and progression of breast cancer. Because relatively little attention has yet to be given to miR-106a, the potential role of miR-106a is often suggested on the basis of a known role of a related family member. Similarly, defined roles of miR-106a and family members in other neoplasms are used to suggest a role in breast cancer.

2. Small interfering RNAs

Interfering RNAs are small ribonucleic acids around 18-25 nucleotides in length. Depending on the author, between 60 and 92% of human genes are likely regulated by these small RNAs (Baek et al. 2008, Dai and Ahmed 2011). Interfering RNAs may be microRNAs (miRNAs) or small interfering RNAs (siRNAs). Both share a similar mechanism of action, but differ in their initial cellular processing. miRNAs are usually encoded by intergenic or intronic regions of DNA, but may be present in exonic regions of non-protein-coding genes or of protein coding genes subject to alternate splicing (Rodriguez et al. 2004 , (Kim et al., 2009). In the classical scheme for their production (Figure 1), miRNA regions of the genome are transcribed by RNA polymerase II as longer sequences including a region that forms a

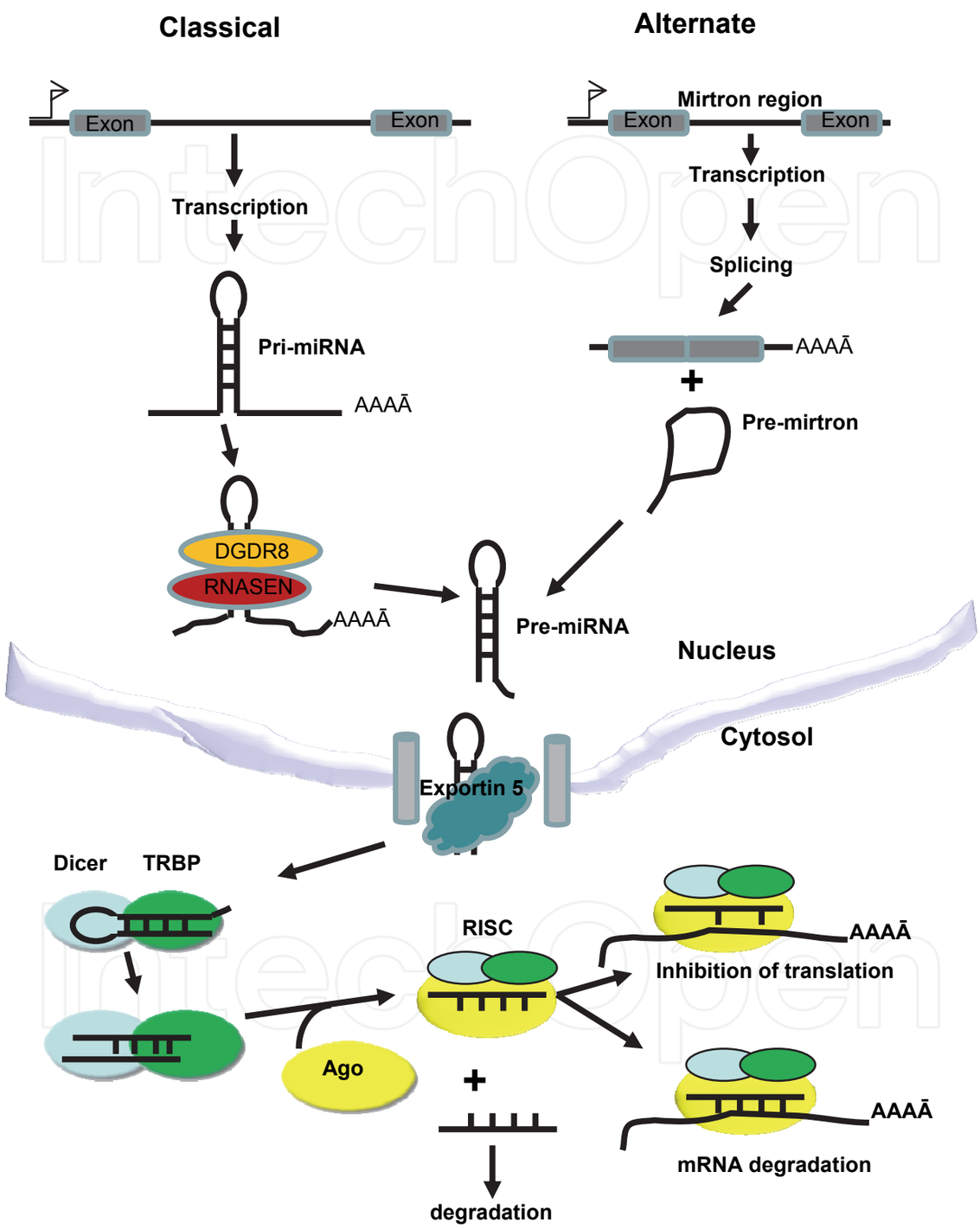

Fig. 1. Classical and alternate pathways of miRNA generation and the mechanisms of inhibition of target gene expression. Figure modified from one by Dai and Ahmed (2011).

hairpin or stem loop (pri-miRNA). This is then processed by binding to DGCR8 (DiGeorge Syndrome Critical Region protein 8) and cleavage by RNASEN (an RNAse III enzyme) to form a pre-miRNA of about 70 nucleotides in length. The pre-miRNA is exported from the nucleus by binding to exportin 5, which recognizes its double-stranded hairpin region. Once in the cytosol, the pre-miRNA is subject to further cleavage by the dicer complex. This removes the loop portion of the hairpin creating two complementary strands of miRNAs. These two strands, along with dicer and a binding protein then interact with Argonaute (Ago) to form RISC (RNA Induced Silencing Complex). One of the complementary strands is released and degraded. The other, now a single-stranded miRNA, is able to bind to its target sequence. At this point, the degree of complementarity between the miRNA and its target sequence determines whether it functions to inhibit translation or promote the degradation of mRNA. The less the complementarity, the more likely it will function to inhibit translation without effect on the level of mRNA. With greater complementarity, miRNAs function more like siRNAs and promote mRNA degradation (Lee et al. 1993, Bartel 2004, Carthew and Sontheimer 2009). To accomplish both of these endpoints, the miRNA binds to the 3′ untranslated region (UTR) of mRNAs (Yekta et al. 2004). Interaction with the 3′UTR relies on a 7 nucleotide "seed sequence" present in the miRNA (see table I).

An alternate pathway for miRNA synthesis exists in which splicing of a small intronic region (a microRNA intron region or mirtron region) out of pre-mRNA creates a lasso-like structure (a pre-mirtron) that subsequently loses its branch to form double-stranded pre-miRNA. This hairpin double-stranded pre-miRNA is then handled in the same manner as the RNASEN-processed variety.

SiRNAs, by contrast, originate via viral infection or are introduced into a cell experimentally. Either way, the cell gains long stretches of double-stranded RNA. These are recognized and bound by specific binding proteins which initiate cleavage by dicer into short 18-25 nucleotide lengths of double-stranded RNA that can interact with Ago. This interaction results in the release and degradation of one strand and the targeting of the specific complementary strand. Since SiRNAs have perfect complementarity, they result in mRNA degradation rather than inhibition of translation.

Having discussed the differences and similarities between these two forms of interfering RNA, focus is now on miRNAs. Although several miRNAs have been proposed to be of importance in breast cancer, the purpose of this review is to draw attention to the potential role of miR-106a.

3. The miR-106a cluster (paralog to miR-106b and miR-17-92 clusters)

To date, the best studied miRNAs implicated in carcinogenesis are in the miR-17-92 family. This family consists of six members : miR-17, miR-18a, miR-19a, miR-20a, miR-19b, and miR-92a. They are all transcribed from the same polycistronic cluster, the miR-17-92 cluster on chromosome 13. In addition in mammals, there are two paralogs, the miR-106b-25 cluster on chromosome 7, and the miR-106a-363 cluster on the X chromosome. These resulted from gene duplications of the miR-17-92 cluster during evolution. As mentioned earlier, miRNAs interact with the 3′UTR of target mRNAs through their seed sequence; hence miRNAs with the same seed sequence may share the same targets. Based on homology of the seed sequences, miRNAs in these paralogous clusters can be grouped into four different families, miR-17,miR-18, miR-19 and miR-92, as shown in table 1.

Seed Sequence	Members in miR-17-92 cluster	Members in miR-106a-363 cluster	Members in miR-106b-25 cluster
AAAGUG (miR-17 family)	miR-17, miR-20a	miR-20b, miR-106a	miR-106b, miR-93
AAGGUG (miR-18 family)	miR-18a	miR-18b	
GUGCAA (miR-19 family)	miR-19a, miR-19b-1	miR-19b-2	
AUUGCA (miR-92 family)	miR-92a-1	miR-92a-2, miR-363	miR-25

Table 1. miRNAs from miR-17-92, miR-106a-363 and miR-106b-25 clusters were grouped into 4 different families based on their seed sequences. Table adapted from Van Haaften et al. (2010).

According to this grouping, miR-106a, for example, may target the same mRNAs as miR-17,miR-20a, miR-20b, miR-106b and miR-93. Tanzer et al.(2004) analyzed the evolutionary history of these miRNAs, a history based on the seed sequence. Interestingly, while an ortholog of the miR-17-92 seed sequence family occurs in Drosophila and C. elegans, both the miR-17 and miR-19 seed sequence families seem to be vertebrate innovations. Moreover, miR-106a seems to exist only in mammals; it was found in mouse, rat, human, and chimp, but not in any non-mammalian vertebrates tested. This raises the possibility of a specific role for miR-106a in mammals where one defining feature is the presence of mammae.

4. Regulation of miRNAs

4.1 Regulation of miRNA by methylation

In addition to protein expression being regulated by miRNAs, formation of miRNAs can be regulated by hypermethylation. Thus, hypermethylation of CpG islands that encompass or are adjacent to miRNA regions can inhibit transcription, as can histone modification (Lehmann et al, 2008). In fact, the frequency of epigenetic regulation of miRNA regions on the genome is estimated to be about an order of magnitude greater than for protein-coding regions. The regions of miRs-124-1, 124-2, 124-3, 126, 141, 148a, 152, 199a-1, 199a-2, 200c, 34a, 663, and 9-1, previously associated with breast cancer, are epigenetically modified, showing an established role for regulation of miRNAs by methylation in breast cancer. The miR-106a region has also been reported to be epigenetically modified in colon cancer (Kunej et al, 2011). Although not yet specifically examined, it is possible therefore that miR-106a is also epigenetically modified in breast cancer, becoming either hypo- or hyper-methylated.

4.2 Regulation of miR-106a by myc and estrogen

In several cancers, upregulation of the oncogene, myc, is accompanied by the induction of many miRNAs, including several members from the miR-17-92, miR-106a-363, and miR-106b-25 clusters (O'Donnell et al. 2005). Evidence that myc directly regulated the expression of these miRNAs was produced by chromatin immunoprecipitation (ChIP). This showed that myc could interact with a fragment upstream of the miR-17-92 cluster. Though there were seven putative myc binding sites (CACGTG) upstream of the miR-106a-363 cluster, no interaction was found in the ChIP assay. However, the expression of miR-106a-363 was

undetectable in their tested cell line, P493-6 B lymphoma cells. Castellano et al. (2009) expanded this study to breast cancer cells and included upstream regulation by estrogen. With estrogen stimulation, expression of myc, and both miR-17-92 and miR-106a-363 clusters was upregulated. There is an estrogen receptor response element 70 bp upstream of the c-myc binding site on the miR-17-92 promoter. However, no detectable interaction between the estrogen receptor and this DNA region was observed. Expression levels of miR106a were too low to make this determination. For miR-17-92, this suggests that estrogen induction of myc preceeds myc induction of the miR-17-92 cluster. Although an indirect induction, it is nevertheless an important link between estrogen, a known oncogene, and the miR-17-92 cluster. miR-106a expression can also be negatively regulated in some cancers. As reported in monocytopoiesis, the transcription factor, acute myeloid leukaemia-1 (AML-1), also known as Runt-related transcription factor 1 (Runx1) can bind to the promoter region of the miR-106a-363 cluster and repress the expression of miR-106a (Fontana et al. 2007).

5. The expression pattern of miR-106a correlates with breast tumor development and other tumor development

Table 2 illustrates the relative expression of miR-106a in tumors versus normal tissue and then in metastasized versus non-metastasized tumors. As can be appreciated, as breast cancer progresses, expression of miR-106a increases. This is also true for several other tumors in which the analysis was carried through to the metastatic stage. Wang et al. (2010), for example, examined breast tumors, matching serum and adjacent normal tissue from patients and showed that miR-106a was consistently and significantly overexpressed in both breast tumors and matching serum samples. The expression was gradually increased as the stage of breast cancer progressed. In addition, the expression was higher in progesterone receptor negative versus positive cancers, as well as in estrogen receptor negative versus ER

Tissue	Expression of miR-106a in tumor compared to non-tumor tissue	Expression of miR-106a in metastasized tumor to non-metastasized tumor
Gastric	Up-regulated	Increased
Colon	Up-regulated	decreased
Renal	Up-regulated	decreased
Pancreas/Liver	Up-regulated	ND
Lung	Up-regulated	Increased
Nervous system	Down-regulated	ND
Prostate	Up-regulated	Increased
Immune	Up-regulated	ND
Breast	Up-regulated	Increased

Table 2. Summary of expression pattern of miR-106a in different tissues and in metastasized tumors. ND, not determined.

positive cancers (Wang et al. 2010). An interesting experiment was performed by Fassan et al. (2009) during which they compared the miRNA expression profiles in male and female breast cancer patients. When compared to female breast tumors, the expression of miR-106a in male tumor samples was downregulated, indicating there might exist a different regulation mechanism between male and female breast cancer, perhaps resulting from a different X chromosome complement (see below).

Macrophages play a dual role in tumor development, acting first to present tumor antigens to T cells that kill transformed cells, and later contributing to tumor progression in a number of different ways (Lamagna et al, 2006). miR-106a inhibits monocyte and therefore macrophage development (Fontana et al 2007). This might be predicted to reduce initial clearing responses to transformed cells and therefore to increase the incidence of breast cancer.

6. Potential significance of X chromosome location of miR-106a

Group B retroviruses, like the mouse mammary tumor, share a common integration site on the X chromosome (Mueller et al. 1992). This is close to the promoter region for the miR-106a cluster. As a result,there is elevated expression of miR-106a.

Irregardless of virus involvement, there are multiple studies indicating reactivation of the silenced X chromosome in breast cancer, particularly basal-like breast cancers (Richardson et al. 2006). Such reactivation could elevate expression of the miR-106a cluster. Some features of the inactive X chromosome (Xi) have been identified. These include hypermethylation of DNA and hypoacetylation of Histones 3 and 4 (Lucchesi et al. 2005). Reactivation of Xi would therefore have to reverse these features. As we will discuss later, it is interesting to note that miR-106a may target SUV420H1, a DNA methyltransferase, and BRMS1-L, a component of the histone deacetylase complex (HDAC). Downregulation of these two proteins by targeting their mRNA by miR-106a would result in DNA hypomethylation and histone acetylation, thereby linking elevated miR106a to the possibility of X chromosome reactivation.

There is also another potential link between breast cancer and X reactivation, in this case related to BRCA1 functionality. Thus, BRCA1 has been reported to regulate Xist transcription from the X chromosome that should be inactive. When transcribed, BRCA1 then guides Xist to reinteract with and therefore re-silence the same chromosome (Ganesan et al., 2004; Ganesan et al., 2002; Silver et al., 2007). However, this is not a universal finding (Pageau et al., 2007; Xiao et al., 2007).

7. Potential targets of miR-106a

Although miR-106a has not been extensively investigated, there are several ways in which reports connect it to an influence on tumor progression. From results derived from a miRNA target search, for example, over 700 potential targets for miR-106a were identified (Sinha et al., 2008). These include cell cycle regulatory proteins, and proteins that regulate apoptosis, angiogenesis, autophagy, metastasis, and drug resistance.

7.1 Involvement in cell cycle regulation and apoptosis

Using a miRNA target search engine, Sinha et al.(2008) proposed that miR-106a had up to 40 targets involved in the regulation of cell proliferation, and up to 44 targets involved in the

regulation of apoptosis (Table 3). Among these targets, the best studied example to date is the tumor suppressor protein, retinoblastoma 1(RB1). RB is a tumor suppressor whose inactivation is involved at some stage in many cancers. Phosphorylation of the Rb protein blocks progression of the cell cycle from G1 to S phase. Inactivation of RB therefore has a proliferative effect. Several studies have shown upregulation of miR-106a was accompanied by downregulation of Rb in a number of different cancers (Zhou et al. 2010, Xiao et al. 2009, Volinia et al. 2006). In addition, RB attenuation also appears to be important in the development of resistance to anti-estrogens, including Tamoxifen (Boscoe et al. 2007, (Lehn et al., 2011), Thangavel et al. 2011). Moreover, therapeutically activating RB has been shown to reestablish cell cycle control in endocrine therapy-resistant breast cancer (Thangavel et al. 2011).

Another important tumor suppressor is p21, also known as cyclin-dependent kinase inhibitor 1 (gene is CDKN1A on table 3). This also regulates cell cycle progression between the G1 and S phase and contains several putative miR-106a sites in its 3′-UTR. The importance of p21 specifically in breast cancer is currently unclear. However, it is widely accepted that loss of function of p21, caused by mutations, reduced expression, or abnormal cellular translocation, would promote breast cancer progression (Trimis et al. 2008, Winters et al. 2003, Balbín et al. 1996). Also, upregulation of miR-106a downregulates p21 expression, and transfection with an antimir of miR-106a restores expression (Ivanovska et al. 2008). Thus, p21 expression is clearly regulated by miR-106a even though direct demonstration of the use of the putative 3′ UTR sites has yet to be reported.

There is a complicated and highly regulated interplay among the many pro- and anti-apoptotic proteins in a cell. Bim (gene called BCL2L11 in table) is a pro-apoptotic molecule, involved in regulating anoikis in the normal developing mammary gland to create a duct lumen (Whelan et al., 2010), as well as responses of breast cancer cells to chemotherapeutics such as paclitaxel (Kutuk and Letai, 2010). Early breast cancer is in many instances characterized by a duct lumen filled with cells that have not undergone normal anoikis. Caspase 6 is the direct activator of caspase 8 in the intrinsic pathway for initiation of apoptosis (Cowling and Downward, 2002). A reduction in expression of Bim, caspase 6 and caspase 8 brought about by elevations of miR-106a would therefore be expected to reduce anoikis/apoptosis leading to increased cell number. Increased proliferation and decreased apoptosis also predict poor prognosis in recurrent breast cancers (Vakkala et al. 1999).

Predicted targets of miR-106a associated with cell proliferation	Predicted targets of miR-106a associated with apoptosis
BCL11B, BCL6, BHLHB3, BMPR2, BTG1,BTG2, BTG3, **CDKN1A**, *COL4A3, CSF1,DERL2, E2F1, EBI3, EDD1, EDG1, EFNB1,EREG, FLT1, FZD3, GAB1, HDAC4, KLF11,LIF, MAP3K11, MAPRE1, PAFAH1B1, PCAF,PDGFRA, PPARD, PTEN, PTHLH, PURB,* **RB1**,*RBBP7, TAL1, TBX3, TGFB1, TOPORS,TSG101, TUSC2*	*ACIN1, ACVR1B, APBB2, APP,* **BCL2L11**,*BCL2L2, BCL6, BIRC4, BNIP2, BTG1,* **CASP6, CASP8**, *CDKN1A, CFLAR, COL4A3, DAPK2,DEDD, DNASE2, DNM2, E2F1, EGLN3,EP300, FASTK, FOXL2, HIF1A, INHBA,LALBA, MAP3K5, PAK7, PIK3R1, PLAGL2,PPARD, PPP2CA, PTEN, PURB, SQSTM1,STK17B, TAOK2, TAX1BP1, TIMP3,TMEM23, TNFRSF21, TOPORS, TP53INP1*

Table 3. Predicted targets of miR-106a involved in cell proliferation and apoptosis. Data from Sinha et al. (2008). Genes in bold type are those chosen as examples in the text.

The activation of oncogenes usually induces cellular apoptosis or senescence as a protective mechanism (Li et al. 2009a, Maes et al. 2008b). In an activated ras oncogene model, it was shown that overexpression of the miR-106a-363 cluster abolished ras-induced senescence. With further deletion analysis, only miR-106a and miR-20b were essential for this function (Hong et al. 2010). The upregulation of miR-106a in cancer therefore might play an important role in inhibition of oncogene-induced senescence, allowing cancer cells to escape this anti-tumor defensive pathway.

7.2 Involvement in metastasis /differentiation of tumors

As shown earlier in table 2, the expression of miR-106a increases with metastasis in breast cancer. This is also true of a number of other cancers and suggests a potential role for miR-106a in the metastatic process. Laminin 5 is a component of the basement membrane that mediates attachment of epithelial cells. Laminin 5 is a direct target of the tumor suppressor, smad4, and increased laminin 5 increases cell adhesion and reduces cancer cell migration (Zapatka et al. 2007). Moreover, epithelial cell interaction with the basement membrane promotes mammary differentiation (McCave et al. 2010). Overexpression of miR-106a down-regulates laminin 5 in the breast cancer cell line, MCF-7, and with an antimir to miR-106a expression is normalized (Wenrich et al. 2007). Thus, reduced laminin 5 is associated with reduced differentiation and reduced cell adhesion to the basement membrane. However, if laminin 5 is cleaved by matrix metalloproteases it becomes a tumor-promoting factor that stimulates cell motility (Carpenter et al. 2009). Thus, the end effect of miR-106a via laminin 5 will depend on the level of matrix metalloprotease activity.

BRMS1L (Breast Cancer Metastasis 1 Like) suppresses metastasis of human breast cancer. It is a component of the mSin3a family of histone deacetylase complexes (HDAC) and therefore suppresses transcription of genes (Meehan et al. 2004). As for the other examples, this protein has a potential binding site for miR-106a on its 3'-UTR. Edmonds et al. (2009) investigated the miRNA expression profile related to expression of the related protein, BRMS1, in breast cancer. Unfortunately, miR-106a was not within their tested array. Given the binding site, however, miR-106a may promote breast cancer metastasis through downregulation of BRMS1-L. Other than this function to suppress metastasis, the related protein, BRMS1, has also been reported to be involved in maintaining sensitivity of breast cancer to chemotherapy (Vaidya et al. 2009).

The protein product of the ARID4A (AT Rich Interactive Domain 4A) gene has been reported to interact with the tumor suppressor proteins, BRMS1 and RB, and therefore to participate in tumor suppression (Hurst et al. 2008). As a predicted target of miR-106a, downregulation of this protein would be expected to promote breast cancer progression.

7.3 Involvement in angiogenesis

The role of miR-106a in angiogenesis is hard to predict from the amount of information currently available. On the one hand, thrombospondin-1 (TSP-1) and connective tissue growth factor (CTGF/CCN2), both anti-angiogenic factors, are targeted by members of the same seed family and therefore would be predicted to be targeted by miR-106a. Downregulation of both contributes to endothelial cell migration and therefore tumor progression (Dews et al. 2006, Chien et al. 2011). On the other hand, vascular endothelial

growth factor (VEGF), one of the most important pro-angiogenic factors (Delli Carpini et al., 2010) also has putative binding sites for miR-106a on the 3'UTR. Hua et al. (2006) made a reporter construct by connecting the 3'UTR of VEGF downstream of a luciferase reporter and then co-transfected this construct into cells with different miRNAs reported to act on this 3'UTR. Among the miRNAs examined (miR-106a, miR-106b, miR-17, miR-20a, miR-20b, miR-150, miR-29b), miR-106a showed the greatest inhibition of luciferase expression (Hua et al. 2006). Further analysis will therefore be required to identify all counterbalancing activities in regard to miR-106a, angiogenesis and breast cancer. All that can be said at present is that both miR-106a and VEGF are increased as a function of breast cancer progression and hence that other factors must influence the interaction between miR-106a and the 3'UTR of VEGF mRNA. PRDM6 (PR/SET Domain Protein 6) is another angiogenesis-related potential target protein. High expression of this protein inhibits endothelial cell proliferation and differentiation (Wu et al. 2008). Down regulation of this protein by miR-106a may initiate breast cancer metastasis through promotion of both endothelial cell differentiation and proliferation.

7.4 Other potential targets in breast cancer

7.4.1 SUV420H1, a DNA methyltransferase

DNA methylation governs the expression of genes and an abnormal epigenetic pattern may contribute to disease. DNA hypomethylation is associated with the worst stages of breast cancer (Soares et al. 1999), and the DNA methyltransferase, SUV420H1, is severely downregulated in human breast cancers (Tryndyak et al. 2006). As mentioned eariler, RB, which forms a complex with this methyltransferase, is also a target of miR-106a. Thus, an elevation of miR-106a would concurrently reduce expression of both RB and the methyltransferase, thereby enhancing hypomethylation.

7.4.2 Atg7 (autophagy-related protein 7)

Autophagy, or self eating, is a lysosomal process that occurs in all cells in order to recycle the components of worn out organelles, to reduce unecessary organelles or cytoplasmic constituents when physiological demands change, or upon cellular stress. Autophagy can serve as a tumor suppressor since defective autophagy provides an oncogenic stimulus, resulting in malignant transformation and spontaneous tumors (Dalby et al. 2010). At the same time, autophagy can function as a cell survival mechanism (Dalby et al. 2010). Atg7 (Autophagy-related protein 7) is a potential target of miR-106a. The effect of reduction in expression of Atg7, as assessed in a knockout mouse model, is increased cell survival (Xue et al. 2010), an effect that would be predicted to contribute to tumor progression.

7.5 Targets related to chemotherapy resistance

Xia et al. (2008) investigated the correlation between miRNA expression and the development of drug resistance in gastric cancers. The data showed that miR-106a was downregulated in the vincristine (VCR)-resistant gastric cancer cell line, SGC7901/VCR (Xia et al. 2008). However, in human breast cancer doxorubicin-resistant MCF-7 cells, there was an upregulation of miR-106a (Kovalchuk et al. 2008). There were no further experiments performed regarding the functional role of this altered expression of miR-106a in either cancer in these papers. Much drug resistance develops through increased expression of

multidrug resistance transporter proteins such as MDR-1. In B cell lymphomas, Fu et al. (2009) examined the relationship between miRNAs and drug resistance. Based on the observation that patients with mantle cell lymphomas (MCL) express higher miR-17-92, he overexpressed miR-17-92 in MCL cells and exposed them to the chemotherapy drug, topotecan. The miR-17-92 overexpressing cells were more resistant to drug treatment. Interestingly, David et al. (2004) found an association between DNA hypomethylation in breast cancer and drug resistance that occurred through regulation of the multidrug resistance protein, MDR-1.

8. miR-106a in development

There are many correlates between early embryogenesis and tumor formation and progression. We therefore sought information concerning the role of miR-106a in development. Foshay et al. (2009) examined the expression of miR-17, miR-20a, miR-106a, and miR-93 (all members of the same seed sequence family) during mouse development. At an early stage of development (E 4.0), both miR-17 and miR-20a were expressed more in the trophectoderm. By contrast, miR-106a was expressed primarily in the inner cell mass, a region considered as the source of stem cells with the potential to differentiate into most cell types. The expression of miR-93 was seen in both the trophectoderm and primitive endoderm. As development progressed (E 6.5), the visceral endoderm had low expression of all four miRNAs, however, the expression of miR-106a and miR-20 was relatively higher. One might speculate therefore that miR-106a expression may be related to stem cell function and differentiation in endoderm-derived tissues. However, in regard to the latter none of the members of the miR-106a-363 cluster, including miR-106a, miR-18b, miR-20b and miR-363, was expressed in early embryonic lung (Lu et al. 2007). The role of miR-106a in development was best described by Ventura et al. who analyzed the consequences of miR-17-92, miR-106a-363 and miR-106b-25 cluster deletion, separately or in combination (Ventura et al. 2008). miR-17-92 deficient mice cannot survive due to severe lung failure. Furthermore, deletion of the miR-17-92 cluster caused defects in B-cell development. However, neither deletion of miR-106b-25 nor miR-106a-363 had any obvious effects. The combined deletion of miR-106b-25 and miR-106a-363 also showed no effect, but the double knockout of miR-106b-25 and miR-17-92 caused more serious problems than deletion of miR-17-92 alone. This analysis either implies a straightforward lack of importance of miR-106a-363 in development or perhaps a degree of subtlety of its effects not easily appreciated. If miR-106a is important to stem cell function, one might predict early tissue aging. Concordant with this suggestion is downregulated expression in human aging (Hackl et al. 2010).

9. Potential roles of miR-106a in other cancers

As shown in table 2, the expression of miR-106a was upregulated in gastric cancer. This was accompanied by low expression of RB1, mentioned previously as a direct target of miR-106a (Zhou et al. 2010, Xiao et al. 2009). Further analysis revealed a positive correlation between miR-106a expression and the stage of tumor-node-metastasis. Higher expression of miR-106a was associated with increasing gastric tumor size, and lymphatic and distant metastasis (Xiao et al. 2009), implying an important role of miR-106a in gastric tumor progression.

In colorectal cancer, miR-106a was overexpressed at both stages I and II, but was decreased at stages III and IV. In addition, high expression of miR-106a was inversely correlated with the cell proliferation-associated target, E2F1 (table 3) (Schetter et al. 2008, Guo et al. 2008). Late stage downregulation of miR-106a predicted shortened disease-free survival. (Díaz et al. 2008).

Slaby et al. (2010) studied miRNA expression in renal cell carcinoma (RCC) versus renal parenchyma from disease-free areas. They found a similar pattern as that described for colorectal cancer i.e. higher levels initially, followed by lower levels when metastasized.

In pancreatic and hepatocellular cancer, miR-106a was upregulated, but no further analysis has yet been performed (Volinia et al. 2006, Kutay et al. 2006).

Primary lung cancer can be classified into 2 types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC is usually diagnosed when the cancer has already spread. The expression of miR-106a is higher in lung cancer compared to non-cancerous regions and higher still in SCLC than NSCLC (Navarro et al. 2009). In addition, it was also shown that patients with higher miR-106a expression had a significantly worse prognosis (Yanaihara et al. 2006).

In vitro analyses have shown that miRNAs in the miR-106a-363 cluster are overexpressed in both Hodgkins lymphoma cells and T cell leukemia (Gibcus et al. 2011, Landais et al. 2007). Targets in leukemia were also identified : myosin regulatory light chain–interacting protein, which regulates actin stress fibers and motility in non-muscle cells, and RB1-like protein, a known tumor suppressor (Landais et al. 2007). $p27^{kip1}$-deficient mice that are highly susceptible to viral infections and develop lymphomas were used to analyze effects in vivo. Among the miRNAs tested (188) that were overexpressed were members of the miR-106a-363 cluster. Their expression was even higher when there was a MMuLV integration at the Xpcl1 locus, the locus responsible for expression of the miR-106a-363 cluster on chromosome X (Kuppers et al. 2011).

In prostate cancer, expression of miR-106a was not merely increased but there was also in incremental increase that correlated with increasing cancer risk. Furthermore, there was a positive correlation between the expression of miR-106a and metastatic status (Moltzahn et al. 2011).

Schulte et al. (2008) examined the expression pattern of miRNAs at different stages of neuroblastoma. However, there was no correlation with the presence or absence of disease or stage of neuroblastoma. In contrast to neuroblastoma, when surgical samples of astrocytoma were compared to adjacent non-astrocytoma tissue, miR-106a was downregulated in astrocytomas when compared to normal tissue. In addition, patients with reduced miR-106a had a lower survival rate. These results imply a rather different and possibly protective role of miR-106a in the brain (Zhi et al. 2010).

10. Conclusion

In this review we have presented experimental, bioinformatic and correlative data and our speculations supporting a role for overexpression of miR-106a in breast cancer. We have discussed the potential role of miR-106a in cell proliferation, apoptosis, metastasis, angiogenesis, gene repression through DNA hypomethylation, and the development of resistance to therapies. From this perspective, we propose that knockdown of miR-106a may be therapeutically beneficial.

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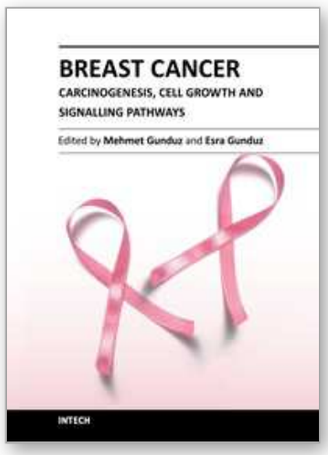

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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